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Graft-versus-Host Disease Is Associated with a Lower Relapse Incidence after Hematopoietic Stem Cell Transplantation in Patients with Acute Lymphoblastic Leukemia

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ABSTRACT

To determine the graft-versus-leukemia effect after hematopoietic stem cell transplantation (HSCT), we studied 199 patients with acute lymphoblastic leukemia who underwent transplantation at Huddinge University Hospital between 1981 and 2001. Seventy-four patients were in first complete remission (CR1), and 125 were in later stages of the disease. Most patients had an HLA-identical sibling donor. Conditioning consisted mainly of total body irradiation and cyclophosphamide, and graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and methotrexate. Acute GVHD developed in 143 patients and chronic GVHD in 67. The 5-year probability of relapse and relapse-free survival (RFS) were 32% and 49%, respectively, in patients in CR1, as compared with 53% and 33% in those with more advanced disease. In the multivariate risk factor analysis of relapse, we found that the absence of chronic GVHD ($P < .001$), absence of herpes simplex virus infection after HSCT ($P = .003$), combination prophylaxis with methotrexate and cyclosporine ($P = .01$), and >6 weeks from the diagnosis to CR ($P = .025$) were independent risk factors for relapse after HSCT. Factors associated with a better relapse-free survival were chronic GVHD ($P < .001$), ABO blood group mismatch ($P = .006$), younger patient age ($P = .01$), and an HLA-matched donor ($P = .01$). The association between herpes simplex virus infection and a low frequency of relapse is a new observation and may indicate that viral antigens play a role in the induction of an antileukemic effect.

KEY WORDS

HSV • GVL • GVHD • HSCT • ALL

INTRODUCTION

Patients with acute lymphoblastic leukemia (ALL) run a higher risk of relapse after hematopoietic stem cell transplantation (HSCT) than those with other hematologic malignancies [1,2]. Graft-versus-host disease (GVHD) is a major complication after HSCT, but it is also closely correlated with the development of the beneficial graft-versus-leukemia (GVL) effect [3-5]. Patients with mild acute or chronic GVHD run a significantly lower risk of leukemia relapse after HSCT than those without GVHD [3-5]. Chronic GVHD is associated with an antileukemia effect and contributes to an improved survival after allogeneic HSCT [3-5]. It is still unclear whether the antitumor effect is mediated by the same or different immune cells as GVHD [1,3,6,7]. The correlation between GVHD and GVL is mainly seen in non–T cell–depleted grafts. In T cell–depleted grafts, the intensity and frequency of GVHD and GVL are markedly reduced [5,8,9]. In this study, we evaluated risk factors for relapse and the GVL effect in 199 patients with ALL who were given HSCT at Huddinge University Hospital between 1981 and 2001.

Table 1. *Patient and Donor Characteristics*

Factor	Data
n	199
Median recipient age (y), range	15 (1-60)
Recipient sex (male/female)	123/76
Median donor age (y), range	25 (2-62)
Donor sex (male/female)	103/96
Donor	
HLA-identical sibling	118 (59%)
HLA-identical related	3 (1.5%)
Mismatched related	12 (6%)
HLA-matched unrelated	50 (25%)
Mismatched unrelated (allele level)	9 (5%)
Mismatched unrelated	7 (3.5%)
Subtypes	
ALL unspecified	22
B-cell ALL	131
T-cell ALL	46
Philadelphia chromosome/4;11 translocation	30/6
Disease stage	
CR1	74 (38%)
CR2	82 (40%)
CR3-5	22 (11%)
Partial remission	10 (5%)
Relapse	11 (5.5%)
Nucleated cell dose (10^8/kg), median (range)	2.9 (0.2-26.9)
Nonimmunized female donor to male recipient	37 (19%)
Immunized female donor to male recipient	19 (9.5%)
ABO blood group compatibility	
Identical	115 (58%)
Minor mismatch	59 (30%)
Major mismatch	25 (13%)
Days from diagnosis to HSCT	378 (53-5224)
Stem cell source (bone marrow/peripheral blood)	176/23
Conditioning	
TBI 10 Gy + cyclophosphamide (Cy)	135 (67%)
TBI 7.5 Gy + Cy	8 (4%)
Fractionated TBI (4 × 3 Gy) + Cy	38 (19%)
Busulfan + Cy	18 (9%)
GVHD prophylaxis	
Methotrexate (MTX)	35 (18%)
Cyclosporine (CsA)	19 (9.5%)
MTX + CsA	126 (63%)
T-cell depletion	14 (7%)
Prednisolone + CsA	4 (2%)
CsA + mycophenolate mofetil	1 (0.5%)
G-CSF after HSCT	74 (37%)

G-CSF indicates granulocyte colony-stimulating factor.

PATIENTS AND MATERIALS

Patients

One hundred ninety-nine patients with ALL underwent HSCT at Huddinge University Hospital between 1981 and 2001 (Table 1). One hundred fourteen (57%) were children younger than 18 years of age, and 85 were adults. Among patients with a mismatched related donor (n = 12), 9 had an HLA-DR–mismatched, 2 an HLA-B–mismatched, and 1 a haplotype-mismatched donor. Among patients with an allele level–mismatched unrelated donor (n = 9), 5 were mismatched at the HLA-B locus and 4 at HLA-DR. Whole-antigen mismatched unrelated donors (n = 7) consisted of 3 HLA-A, 2 HLA-B, and 2 HLA-DR mismatches.

Before the transplantation, 53 (42%) of 125 patients beyond first complete remission (CR1) had a relapse while still receiving therapy, 33 had high leukocyte counts (>100 × 10^9/L) at diagnosis, and 72 were considered to be slow responders, defined as >6 weeks from the diagnosis to their first CR. Among the children, 25% were in CR1, as compared with 55% of the adults. Children who underwent transplantation in CR1 had high-risk criteria, such as the Philadelphia chromosome (n = 7), the 4:11 translocation (n = 1), or a high leukocyte count at diagnosis (n = 4) or were slow responders (n = 2).

Conditioning

Most of the patients received cyclophosphamide (Cy) 60 mg/kg on 2 consecutive days combined with 10 Gy of total body irradiation (TBI), with the lungs shielded to receive no more than 9 Gy (Table 1) [10]. Thirty-eight patients were treated with fractionated TBI 3 Gy for 4 days combined with Cy 120 mg/kg. Eight patients given a T cell–depleted graft were conditioned with Cy 120 mg/kg and 3 × 2 Gy of total lymph node irradiation, followed by 7.5 Gy of TBI [11]. Eighteen patients received busulfan (4 mg/kg/d × 4) and Cy (60 mg/kg × 2) [12].

Matched unrelated donor (MUD) recipients received 3 to 5 days of treatment (days −5 to −1) with either antithymocyte globulin (IMTIX-Sangstat, Lyon, France, or Fresenius AG, Gräfelfing, Germany) in a dose of 2 to 5 mg/kg/d or OKT-3 (Janssen-Cilag, Zug, Switzerland) 5 mg/d before transplantation [13]. All patients were given 2 doses of intrathecal methotrexate (MTX) 12 mg or cytarabine 30 mg before HSCT.

GVHD Prophylaxis

Most patients received cyclosporine (CsA) combined with a short course of MTX [14,15]. Intravenous CsA in a dose ranging from 5 to 10 mg/kg/d was started on day −1 in patients with MUD and from 1 to 3 mg/kg/d in patients with HLA-identical sibling donors. During the first month, blood CsA levels were kept at 200 to 300 ng/mL in those with MUD and at approximately 100 ng/mL in those with sibling donors [16]. After 6 months, in MUD transplant recipients, the CsA dose was decreased by 25% every alternate month and discontinued after 12 months in the absence of GVHD. In sibling transplant recipients, CsA was discontinued after 3 to 6 months. Fourteen patients with an HLA-mismatched graft received a T cell–depleted graft and no immunosuppression after transplantation [11]. Other protocols included CsA

combined with steroids or mycophenolate mofetil [17]. Some patients received MTX or CsA alone, as described in detail elsewhere [18].

Definitions

Bone marrow (BM) aspirates were taken at 3, 6, and 12 months and then yearly after HSCT. Regenerating peripheral blood values were considered as clinical remission when <5% blasts per 200 nucleated cells were found.

Leukemic relapse was defined as >30% blasts in BM or extramedullary leukemic cells—ie, extramedullary relapse. The presence of 5% to 30% blasts in the marrow was regarded as an early relapse. Molecular relapse was considered as increasing levels of BCR/ABL transcript in the peripheral blood, BM samples in Philadelphia chromosome–positive ALL, or increasing levels of recipient cells in the leukemia-affected cell lineage [19]. A herpes simplex virus (HSV) infection was defined as a positive HSV isolation or positive immunofluorescence from lesions or a positive polymerase chain reaction (PCR).

Diagnosis and Treatment of GVHD

Acute GVHD was diagnosed on the basis of clinical symptoms or biopsy samples of skin, oral mucosa, liver, and gut. GVHD was graded from 0 to IV [20]. At the first sign of grade I GVHD, prednisolone 2 mg/kg/d was given [21]. Severe or persistent GVHD was treated with antithymocyte globulin [22] or psoralen and ultraviolet light [23,24]. Chronic GVHD was diagnosed on the basis of clinical symptoms or biopsy samples from the skin, oral mucosa, liver, and gut.

Stem Cell Source and Supportive Care

One hundred seventy-six patients received BM, and 23 received stem cells from peripheral blood. Granulocyte colony-stimulating factor was given to 74 (37%) of the patients from day 10 after HSCT until the absolute neutrophil count reached $>0.5 \times 10^9$/L for 2 consecutive days [25]. Since 1986, prophylaxis with acyclovir (ACV), 200 mg × 4 by mouth daily until day 30 after HSCT, has been given to all patients with an HSV serotiter of >10000. Before 1986, a few patients included in a randomized study received ACV as prophylaxis. Some patients were also included in a cytomegalovirus prophylactic study that compared ACV and valacyclovir in various doses.

HLA Typing

Before 1997, HLA class I typing was serologic. Since then, we have used PCR sequence-specific primer low-resolution typing for class I. Since July 1992, the PCR methods with sequence-specific primer pairs have been used [26]. All patients with unrelated donors have recently been retrospectively retyped by using PCR sequence-specific primer high-resolution typing for both HLA class I and II antigens [27].

Statistics

The time to relapse was determined with the life table method by using the log-rank (Mantel-Haenszel) test, taking censored data into account. The Cox regression model was used for the univariate and multivariate analyses [28]. The time to relapse was used to calculate the cumulative incidence curves, and death was a censored observation, unless relapse had occurred. When relapse was analyzed, patients who died within 90 days of HSCT without a relapse were excluded. Thirty-two risk factors for relapse were studied (Table 2). Only factors at ≤10% levels in the univariate analyses were introduced into the stepwise elimination multivariate analysis. We performed only 1 multivariate analysis for each event. Therefore, no Bonferroni correction was performed. A female donor was considered to be immunized if she had been pregnant or had had a blood transfusion. Patients in CR1 were considered to have early disease, and all other stages were considered to be late diseases.

RESULTS

Graft-versus-Host Disease

Six patients died within 30 days of HSCT without acute GVHD and were not included in the analysis of acute GVHD. Fifty patients (26%) had no sign of acute GVHD. Of the remaining patients, 98 (51%) developed grade I, 30 (16%) grade II, and 15 (8%) grade III or IV. The cumulative incidences of acute GVHD grades II to IV were 17%, 28%, and 40% in grafts from HLA-identical siblings, MUD, or HLA-mismatched donors, respectively. The corresponding figures for chronic GVHD were 48%, 52%, and 41%.

Relapse

Twenty patients died within 90 days of HSCT. Recurrent disease was diagnosed in 70 (68 morphologically and 2 molecularly) of the 179 remaining patients. Fifty-one (73%) of the relapses occurred within 1 year of HSCT. The cumulative probability of relapse was 32% at 5 years in patients with early disease and 53% in those with advanced disease ($P < .01$). The probabilities of relapse in patients with an HLA-identical sibling donor, mismatched related donor, MUD, and mismatched unrelated donor were 38%, 53%, 48%, and 68%, respectively.

Risk Factors for Relapse

In the Cox regression univariate analysis, 6 factors were significant at the 5% level. We also included 3

Table 2. *Cox Regression: Univariate Analysis of Risk Factors for Relapse and Relapse or Death (RFS) in 199 HSCT Patients with Acute Lymphoblastic Leukemia*

Factor	No/Yes	Relapse *P* Value	RFS *P* Value
Recipient sex	Male/female	.64	.78
Recipient age	In decades	.71	.01
Donor	Others/sibling	.16	.24
	Related/unrelated	.31	.84
HLA match	Match/mismatch	.13	.002
Disease status	CR1/>CR1	.01	.01
	Remission/no remission	.22	.40
HSCT year	5-y increments	.06	.63
Nucleated cell dose ($\times 10^8$/kg)	<2.9/>2.9	.70	.28
ABO	Match/mismatch	.20	.02
Donor sex	Male/female	.36	.27
Donor age	In decades	.51	.09
Conditioning	TBI/busulfan	.72	.98
	Others/fTBI	.07	.25
GVHD prophylaxis	Monotherapy/combination	.10	.55
Prophylaxis	Others/TcD	.65	.99
Time from diagnosis to HSCT	<1/≥1 y	.07	.16
Female donor to male recipient	No/yes	.53	.32
Immunized female donor to male	No/yes	.56	.05
Stem cell source	BM/PBSC	.82	.92
G-CSF after HSCT	No/yes	.24	.89
Acute GVHD	No/yes	.009	.04
	0-I/II-IV	.05	.29
Chronic GVHD	No/yes	<.001	<.001
HSV infection	No/yes	.002	.04
CMV infection	No/yes	.84	.63
Ph^+ or t(4;11)	No/yes	.92	.79
Relapse on therapy	No/yes	.22	.007
Leukocyte count at diagnosis	<100/>100 × 10^9/L	.45	.53
Time from diagnosis to CR	<6/>6 wk	.028	.11
Recipient CMV serostatus	−/+	.77	.26
Donor CMV serostatus	−/+	.52	.22

CR indicates complete remission; HSCT, hematopoietic stem cell transplantation; ABO, blood groups; TBI, total body irradiation; fTBI, fractionated TBI; GVHD, graft-versus-host disease; G-CSF, granulocyte colony-stimulating factor; HSV, herpes simplex virus; CMV, cytomegalovirus; TcD, T-cell depletion; Ph^+, Philadelphia chromosome positive; PBSC, peripheral blood stem cells.

additional factors significant at the 10% level in the multivariate analysis (Table 2). In the stepwise elimination multivariate analysis, stratified for disease stage and corrected for transplantation year and occurrence of the t(9;22) or t(4;11) translocations, the absence of chronic GVHD ($P < .001$), absence of HSV infection ($P = .003$), GVHD prophylaxis with CsA and MTX ($P = .01$), and being a slow responder ($P = .025$) were independent risk factors for relapse in this study (Table 3). If chronic GVHD was not included in the analysis, absence of HSV infection (hazard ratio [HR], 6.30; 95% confidence interval [CI], 1.98-20.0; $P = .002$) and being a slow responder (HR, 1.84; 95% CI, 1.06-3.19; $P = .03$) were independent risk factors for relapse. The probability of relapse in patients with or without chronic GVHD, in patients with and without an HSV infection, those with monotherapy versus combination prophylaxis, and slow responders versus rapid responders is shown in Figure 1. The relapse rates did not differ between B-lineage (43%) and T-lineage (49%) ALL. The probability of relapse among patients with Philadelphia chromosome–positive or t(4;11) ALL in CR1 (n = 24) was 46%, as compared with 25% in patients (in CR1) without these translocations (n = 46; $P = .08$).

Table 3. *Results of the Multivariate Analysis of Factors Associated with Relapse and Treatment Failure Stratified for Disease Stage and Corrected for Transplantation Year and Occurrence of the t(9;22) and t(4;11) Translocations*

Factor	HR	95% CI	*P* Value
Relapse			
No chronic GVHD	3.82	1.82-8.00	<.001
No HSV infection	6.17	1.82-20.9	.003
Combination GVHD prophylaxis	2.56	1.22-5.37	.01
Slow responder	1.95	1.07-3.56	.025
RFS			
No chronic GVHD	2.59	1.65-4.06	<.001
ABO match	1.82	1.19-2.86	.006
HLA mismatch	2.08	1.20-3.60	.01
Higher recipient age	1.19	1.03-1.36	.01

CI indicates confidence interval; HR = hazard ratio.

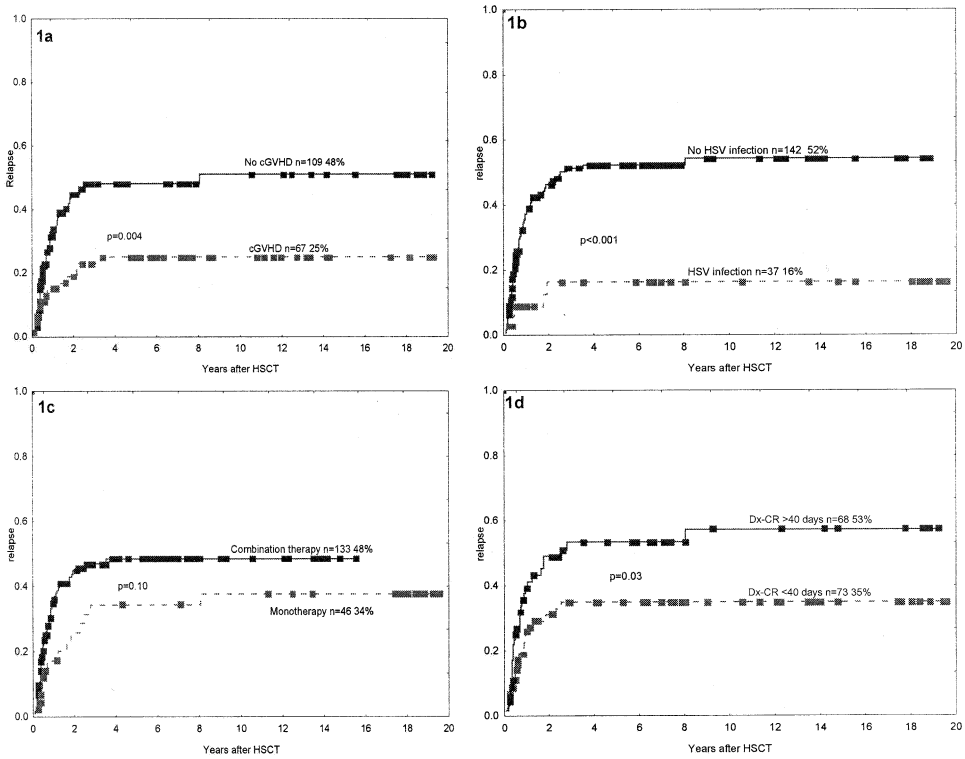

Figure 1. Probability of relapse in patients with or without 4 risk factors for relapse after HSCT for ALL: (a) chronic GVHD, (b) herpes simplex virus infection, (c) GVHD prophylaxis, and (d) time to initial response on therapy after diagnosis (univariate comparisons). In (a), all patients were initially included in the non-GVHD arm. Once they developed GVHD, they were moved into the GVHD arm (left truncated figure).

Relapse-Free Survival

Relapse-free survival (RFS) in all patients was 39%. Among patients with a sibling donor or a MUD, RFS was 41% and 43% at 5 years, respectively. In patients with a mismatched related or unrelated donor, the corresponding figures were 25% and 19%, respectively.

In the univariate analysis of RFS, we found 9 factors to be significant at the 5% level and 1 factor at the 10% level (Table 2). In the multivariate analysis, chronic GVHD ($P < .001$), an ABO blood group antigen–mismatched graft ($P = .006$), younger patient age ($P = .01$), and an HLA-matched donor ($P = .01$) correlated with a better RFS (Table 3). When chronic GVHD was excluded, factors correlated with better RFS were an HLA-matched donor (HR, 1.97; $P = .004$), lower patient age (HR, 1.25; $P = .003$), CR1 (HR, 1.79; $P = .006$), and an ABO-mismatched graft (HR, 1.49; $P = .04$; Figure 2). Improved RFS was mainly seen in minor ABO mismatches (antirecipient hemagglutinins in the donor). Patients with an ABO-mismatched donor had a trend for lower relapse rates (38% versus 50%; $P = .2$) and a lower nonrelapse mortality (21% versus 34%; $P = .04$) than those with an ABO-matched donor.

HSV Infection

A total of 40 (20%) patients had a documented HSV infection after HSCT. None of the patients had a life-threatening HSV infection. Three of these patients died before day 90. Fifty-six patients were seronegative and 140 were seropositive for HSV at transplantation. Among the seropositive patients, 53 had high titers (≥10000), and 81 had low titers. In 6 patients, the HSV titer was not available. An HSV infection occurred more frequently among the seropositive patients than seronegative ones (26% versus 5%; $P = .002$). The seropositive patients with high titers had significantly more HSV infections than the low-titer patients (43% versus 16%; $P = .001$). Since 1986, when we started to give ACV prophylaxis, the incidence of HSV infections has declined among patients with high pretransplantation HSV titers, and infections occur later. In this patient population, no correlation was found between HSV serostatus and relapse. The median number of days to HSV infection did not differ between patients with or without a relapse (26 versus 41 days, respectively). An HSV infection was more common in adults than in children (28% versus 14%; $P = .02$). The effects of an HSV infection and chronic GVHD on various outcome variables are shown in Table 4.

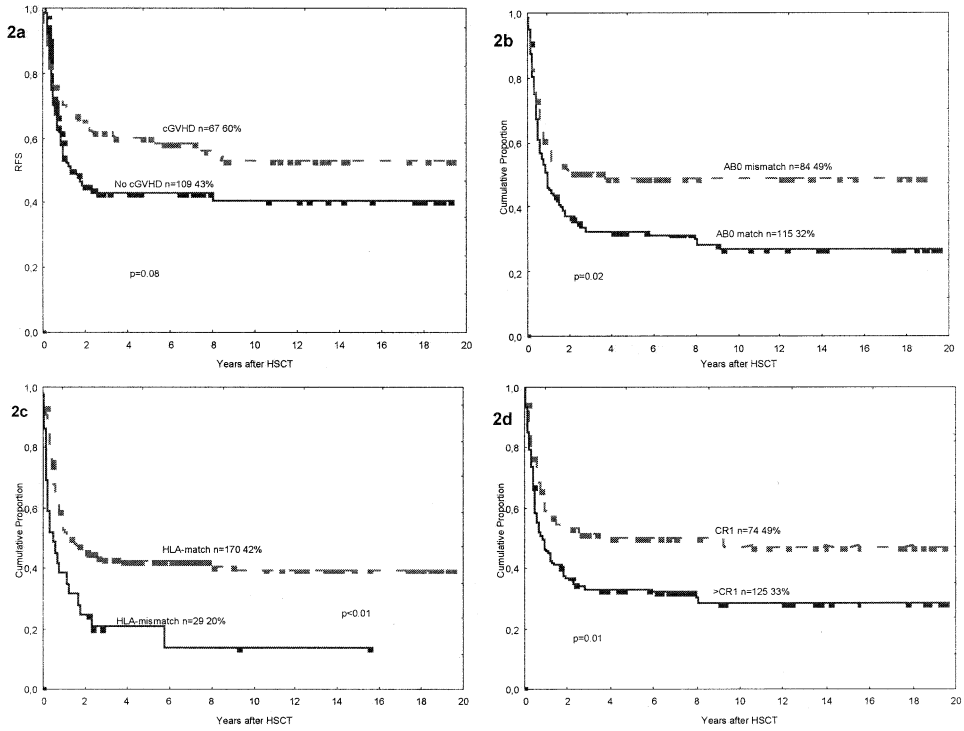

Figure 2. Probability of relapse-free survival in patients with or without 4 risk factors for treatment failure after HSCT for ALL: (a) chronic GVHD, (b) ABO blood group compatibility, (c) HLA match, and (d) disease stage at transplantation (univariate comparisons). In (a), all patients were initially included in the non-GVHD arm. Once they developed GVHD, they were moved into the GVHD arm (left truncated figure).

Donor Lymphocyte Infusion Treatment

Eleven of the patients who relapsed were treated with a donor lymphocyte infusion (DLI). Nine of these patients had a morphologic relapse, and 2 had a molecular relapse. Four (36%) patients responded, but 1 relapsed again after a short remission (2 months); the others remain in remission 16 to 28 months after the DLI. Of the 4 who responded, 3 had a morphologic relapse and 1 a molecular relapse. Among the 11 DLI-treated patients, 8 had no acute GVHD, 1 developed grade I, 1 developed grade II, and 1 developed grade IV acute GVHD. Chronic GVHD developed in 5 patients. Another 9 patients who relapsed received a second transplant from the same donor. Eight of them died a median of 64 days (range, 5 days to 2.7 years) after the second transplantation. The surviving patient is in complete remission after 3 years. The median time from the first transplantation to relapse was 1.9 years (range, 0.3-3.6 years), and the median time from relapse to a second transplantation was 68 days (range, 33-155 days). Four of the patients who underwent retransplantation died when they relapsed after the second transplantation. Other causes of death in this group were 1 each of fungal infection, interstitial pneumonia, acute GVHD, and lung edema.

Table 4. *The Effects of HSV Infection and Chronic GVHD on Outcome after HSCT in Patients with ALL: Actuarial 5-Year Probabilities*

HSV Infection	Chronic GVHD	n	TRM	Survival	Relapse	RFS
No	No	91	19%	30%	62%	30%
Yes	No	19	31%	49%	26%	50%
No	Yes	48	16%	60%	32%	57%
Yes	Yes	18	26%	74%	7%	68%

TRM indicates transplant-related mortality; RFS, relapse-free survival.

DISCUSSION

The role of GVL in ALL is uncertain. Some studies report little, if any, effect of an acute GVHD alone, whereas others have found a lower incidence of relapse after acute or chronic GVHD, or both, than with no GVHD and have found that chronic GVHD has a stronger antileukemia effect than acute GVHD [2-5,29-33].

Because chemotherapy is curative in most children with ALL, only the most severe cases undergo transplantation, and these account for a high relapse rate. It has recently been shown that many of the patients with ALL considered to be in complete remission had high levels of minimal residual disease, which is also associated with an increase in the relapse rate [34,35].

This may indicate that ALL is less responsive to a GVL effect than other hematologic malignancies or that the GVL effect may not have the time to arrest a rapidly developing disease in acute leukemia patients with minimal residual disease before the transplantation.

We found that GVHD and the type of GVHD prophylaxis affected the incidence of relapse. This has been reported previously [3-5,36,37]. However, with better immune prophylaxis, the GVHD-associated mortality is reduced and results in unaffected RFS.

An association between herpes virus serology and GVHD was reported [38,39]. The correlation between an HSV infection and a lower risk of relapse could be indirect and due to GVHD. However, we found a similar incidence of both acute and chronic GVHD in patients with or without an HSV infection. Moreover, in the multivariate analysis, the correlation between an HSV infection and a lower incidence of relapse was independent of GVHD. Another explanation may be that HSV infections have an antileukemia effect. Using an animal model, Toda et al. [40] showed that the inoculation of tumor cells with HSV virus inhibited tumor growth by local cytotoxic viral replication initiating a systemic antitumor immune response. Other studies have found that replication-competent HSV-1 is cytolytic to tumor cells and thus inhibits tumor growth in vivo in both immune-deficient and immune-competent animals [41-44]. This could be due to the lytic destruction of tumor cells releasing tumor antigens that are picked up by antigen-presenting cells and carried to the draining lymph nodes, where they are processed and presented to $CD8^+$ T cells. Associative recognition of HSV-specific and tumor-specific antigens may also play a role in the strength of the response. HSV-infected tumor cells would have maturing virions budding from their cell membranes and may also process viral antigens for MHC class I presentation, like antigen-presenting cells. The HSV-infected tumor cells could, therefore, directly induce T cell–mediated immune reactions. Some of the immune response induced by co-presentation of viral and tumor antigens may be triggered thereafter by only 1 of the coexpressed antigens. Our data suggest that HSV replication after HSCT may induce leukemia cell lysis, a systemic immune response against malignant cells, or both, possibly through T or natural killer cells. However, this hypothesis must be proven in appropriate experiments. Patient age, pretransplantation HSV serology, and a more toxic conditioning regimen may serve as surrogate factors for an HSV infection, but the inclusion of these surrogate factors in the multivariate analysis did not change the results.

In this study, we also evaluated well-known high-risk criteria, such as "slow responder," high leukocyte count at diagnosis, relapse while still on therapy, and 9;22 or 4;11 translocation. Patients who were considered to be slow responders ran a significantly higher risk of relapse after transplantation than those who responded more quickly (53% versus 35%; $P = .03$; Figure 1). This association was still apparent in the multivariate analysis ($P = .03$). These patients may have a more resistant disease in which the conditioning therapy and the GVL effect are less potent.

We found an association between ABO blood group mismatch and better RFS. This is controversial but is in line with Metha et al. [45], who reported an association between ABO mismatch and a lower relapse rate and better overall and disease-free survival in BM transplantation patients with acute myeloid leukemia.

An association between higher patient age and worse RFS was found. This is well known; older patients are more susceptible to toxic effects from the conditioning and do not tolerate GVHD and its treatment as well as younger patients.

We found an association between an HLA-mismatched graft and a worse RFS, but there was no association with relapse. One would think that patients with mismatched or unrelated donors would run a higher risk of GVHD and, therefore, have a lower risk of relapse. However, many patients with a mismatched donor received a T cell–depleted graft. T-cell depletion entails a lower risk of GVHD but a higher risk of relapse and infections, a slower immune reconstitution, and lower survival [46,47].

The response rates to DLI depend on the time of relapse, disease, induction of GVHD, and grade of disease at treatment [48]. The best results have been found in patients with chronic myeloid leukemia, whereas ALL patients have very low response rates [49,50], suggesting a limited GVL effect in this group of patients. However, in our study, DLI treatment induced remission in 4 (36%) of 11 treated patients, as was also shown by Slavin et al. [51]. Therefore, DLI treatment in patients with relapsed ALL after HSCT may be effective in some patients.

We conclude that chronic GVHD and HSV infection were associated with a lower relapse rate, whereas more effective GVHD prophylaxis and being a slow responder were associated with a higher rate. The association between an HSV infection and fewer relapses is a new observation and may indicate a role of viral antigens in the induction of an antileukemic effect. However, the retrospective nature of this analysis, coupled with the 20-year span, increases the need for caution in interpreting these findings.

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